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Motor function in adults of an Ohio community with environmental manganese exposure

Yangho Kim [a,*], Rosemarie M. Bowler [b], Nadia Abdelouahab [c], Matthew Harris [d], Vihra Gocheva [b], Harry A. Roels [e]

[a] Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, # 290-3 Cheonha-Dong, Dong-Gu, Ulsan 682-060, South Korea
[b] San Francisco State University, Department of Psychology, San Francisco, CA 94132, United States
[c] University of Sherbrooke, Quebec, Canada
[d] Alliant International University, San Francisco, CA 94132, United States
[e] Louvain Centre for Toxicology and Applied Pharmacology, Université catholique de Louvain (Brussels), J. Pauwelslaan 3, B-3271 Averbode, Belgium

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ABSTRACT

Objectives: The objective of the present study was to evaluate motor function in order to assess the effects of long-term, low-level environmental manganese (Mn) exposure in residents of an Ohio community where a large ferro- and silico-Mn smelter has been active for more than 50 years.
Methods: One hundred residents from the Mn-exposed Ohio community were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), a postural sway test, and a comprehensive questionnaire exploring demographics and general health. The results were compared to those of 90 residents from a demographically similar comparison town in Ohio. Mn exposure was assessed using modeled airborne Mn and blood Mn (Mn-B). The UPDRS was employed to evaluate parkinsonian motor features. Postural sway was measured using a CATSYS 2000 (Danish Product Development).
Results: No significant difference between the exposed and comparison groups was evident as to Mn-B, demographics or major health outcomes. The risk of abnormal UPDRS performance using "Motor and Bradykinesia" criteria was increased in the Mn-exposed group after adjustment for potential confounders such as the presence of other neurotoxic metals, factors affecting susceptibility to Mn, potential factors influencing motor performance, and other possible demographic confounders. No participant was diagnosed with clinical manganism by neurological examination. After adjustment for various potential confounders, the Mn-exposed group showed significantly higher postural sway scores under eyes-open conditions than the comparison group.
Conclusions: Subclinical findings on the UPDRS and postural sway in the Mn-exposed group may possibly reflect early subtle effects of chronic low-level Mn exposure. However, the cross-sectional study design, the small to medium effect sizes, and the little biological plausibility are limiting the possibility of a causal relationship between the environmental Mn-air exposure and the early subclinical neurotoxic effects observed.

1. Introduction

Exposure to high levels of manganese (Mn) in occupational environments may affect health, causing symptoms similar to those of Parkinson's disease (PD) with neurological and neuropsychological sequelae. The syndrome has been termed "manganism" and can occur following long-term airborne Mn (Mn-air) exposure that is usually higher than 2 mg/m^3, but susceptible individuals may develop clinical features after exposure to levels as low as 1 mg/m^3 (WHO, 1981). At lower exposure levels, less severe, preclinical neurobehavioral effects have been widely reported in various occupational settings (Bast-Pettersen et al., 2004; Bowler et al., 2007b; Iregren, 1999; Lucchini et al., 1999; Mergler et al., 1994; Roels et al., 1987, 1992, 1999). The main adverse manifestations are dose-related impairment of motor function, a negative effect on mood, cognitive deficits, and reduced coordination (Iregren, 1999; Levy and Nassetta, 2003; Zoni et al., 2007).

Little is known, however, about the possible neurobehavioral effects of environmental exposure to Mn-air. A community study conducted in Mexican villages close to Mn extraction and refining plants showed average Mn-air concentrations of 0.10 μg/m^3 in the mining village and 0.03 μg/m^3 in a reference

* Corresponding author. Tel.: +82 52 250 7281; fax: +82 52 250 7289.
E-mail address: yanghokm@nuri.net (Y. Kim).

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village. In a Mn-exposed group, neurobehavioral testing revealed dose-dependent alterations in motor and cognitive functions (Rodriguez-Agudelo et al., 2006). In a Canadian community study, Mergler et al. (1999) found an association between decreased neurobehavioral function and higher Mn concentration in blood (Mn-B), although Mn-air levels were low (Baldwin et al., 1999). Two ecological population studies addressed the potential influence of environmental Mn exposure on the prevalence of parkinsonian disorders (Lucchini et al., 2007) or PD (Finkelstein and Jerrett, 2007), respectively in the Brescia province (Italy) and Ontario (Canada). Recently, two reports have appeared on residents exposed to environmental Mn in an Ohio community (USA) (Haynes et al., 2010; Standridge et al., 2008). The latter authors reported an effect of chronic low-level Mn exposure on postural balance. Haynes et al. (2010) reported a relationship between hair Mn level in residents and modeled ambient Mn-air concentration.

The Unified Parkinson's Disease Rating Scale (UPDRS) was originally developed in the 1980s (Fahn et al., 1987) and has become the most widely used clinical modality for assessing parkinsonian motor impairment and disability (Movement Disorder Society Task Force, 2003; Ramaker et al., 2002). The scale which was used in the present work is officially termed UPDRS Version 3.0 (Fahn et al., 1987). The scale has four components: Part I, "Mentation, Behavior and Mood"; part II, "Activities of Daily Living (ADL)"; part III, "Motor"; and part IV, "Complications". One of the core advantages of the UPDRS is that it was developed as a compound scale to capture multiple aspects of PD. The scale assesses both motor disability (part II: UPDRS ADL) and motor impairment (part III: UPDRS Motor). In addition, part I addresses mental dysfunction and mood, whereas part IV explores treatment-related motor and non-motor complications (Ramaker et al., 2002). Although specifically developed to assess PD, the UPDRS has also been used to rate parkinsonian features of other conditions, including those of normal aging, progressive supranuclear palsy, Lewy body dementia, and manganism (Ballard et al., 1997; Bennett et al., 1997; Beuter et al., 1999; Cubo et al., 2000; Koller et al., 2004; Lazeyras et al., 2002; Sikk et al., 2007).

Postural balance testing has proven to be useful in identifying subclinical neuromotor abnormalities occurring secondary to exposure to various neurotoxicants (Bhattacharya, 1999; Bhattacharya et al., 1990, 2006; Kuo et al., 1996; Sack et al., 1993; Smith et al., 1997). Several occupational studies have utilized postural balance testing in the context of Mn exposure (Bowler et al., 2007a,b; Chang et al., 2009; Chia et al., 1993, 1995; Kaji et al., 1993; Kim et al., 2007; Young et al., 2005). Only two previous reports have evaluated the influence of chronic non-occupational Mn exposure on postural balance (Hudnell, 1999; Standridge et al., 2008).

In Marietta, OH, community groups have expressed health concerns over continued industrial Mn pollution caused by a facility operated by Eramet Marietta Inc. (EMI). EMI has produced ferro- and silico-Mn for the steel industry commencing in the early 1950s, and historically high levels of Mn-air emissions were recorded in the first decades of operation (US-EPA, 1984). The present cross-sectional study sought to assess subclinical health effects, potentially associated with Mn-air emissions, in the Marietta community. Mount Vernon, OH, was selected as a comparison town because of demographic similarity to Marietta (U.S. Census Bureau, 2001a,b) as well as the lack of any major industry (US-EPA, 2010b).

The objective of the present study was to assess whether long-term low-level environmental Mn-air exposure in residents of an Ohio community is associated with impairment of motor function evaluated using the UPDRS Motor and ADL subscales and a postural sway test.

2. Methods

2.1. Participants

Subjects who had lived for at least 10 years in the Mn-exposed town (Marietta, Washington County, OH) or the comparison town (Mount Vernon, Knox County, OH), and who were 30–75 years of age, were recruited. A random selection design was chosen to enhance generalizability of results. A maximum of two eligible members were recruited from each selected household. Exclusion criteria included a work history at EMI; a history of having lived in Marietta for Mount Vernon participants; the presence of a neurodegenerative disease (multiple sclerosis, Alzheimer's dementia, Huntington's chorea, or PD); a history of a brain ailment (meningitis, encephalitis, stroke requiring hospitalization for more than 1 day, a condition requiring brain surgery, any prior head injury, or epilepsy); a history of a serious psychiatric condition (schizophrenia, any major psychiatric diagnosis, or bipolar disorder); current treatment with anticonvulsive drugs; alcohol/drug dependence; a history of a hepatic condition; pregnancy; current nursing status; being medically unfit to participate in the study; or a history of exposure to hazardous chemicals (pesticides, fungicides, herbicides, carbon monoxide, and/or neurotoxic metals).

In Marietta, a total of 1732 invitation letters were mailed to randomly selected households of whom 264 individuals expressed interest and 122 were eligible for testing. In Mount Vernon, 2297 invitation letters were sent, 245 individuals expressed interest, and 117 were eligible. In all, 270 respondents to the random mailings were excluded on the basis of our exclusion criteria, or were unable to participate. Of the 239 subjects who were both interested and eligible, 191 participants (exposed: $n = 100$, comparison: $n = 91$) from 150 households (exposed: $n = 76$, comparison: $n = 74$) were tested. One participant from the comparison town was excluded after testing because of inadequate residency duration. Thus, data from 100 Mn-exposed and 90 comparison participants were available for analysis.

The Ohio Department of Health (ODH), the US and Ohio Environmental Protection Agencies (EPAs), and the Agency for Toxic Substances and Disease Registry (ATSDR) provided technical assistance, input into the study design, and review of the San Francisco State University (SFSU) protocol. The institutional review boards of SFSU and the ODH each granted research approval. Written informed consent was obtained from each participant prior to testing. Data collection occurred during August 2009.

2.2. Exposure assessment in Marietta, OH

High-temperature industrial processes such as smelting and steel production are significant sources of fine particles that are enriched with toxic metals (Schroeder et al., 1987) and which have the potential of causing contamination of the environment with airborne fine particulate. This has been recognized for the Marietta site in health consultation reports (ATSDR, 2009) which show levels of ambient air Mn that exceed the RfC of 0.050 $\mu g/m^3$ (US-EPA, 1993) derived for respirable particulate. Using 2001 Mn-air emission data, the US-EPA performed Mn-air dispersion modeling for the Marietta area as a part of the present study. Deposition was not included in the model. The AERMOD modeling system (US-EPA, 2009b) also included terrain information, and 1994–1998 surface and upper air meteorological data from the records of weather service stations located at the Parkersburg (WV) airport and in Dayton (OH), respectively (NOAA, 2010; USGS, 2010; WebMET, 2010). A geographic information system grid overlay was created to map Mn-air exposure (respirable particulate only) within the study area. An annual average Mn-air concentration, in $\mu g/m^3$, was

calculated for each 10 m × 10 m grid cell using the centroid as a proxy receptor for actual residences located therein.

2.3. Neurologic examination

The UPDRS has been used for assessment of parkinsonian motor and neurological impairment, and the resulting disabilities. The UPDRS ADL and UPDRS Motor subscales were employed in the present study. The UPDRS ADL questionnaire contains 16 items, and the scoring scale for each item ranges from 0 to 4, where a higher score indicates a more severe problem. The UPDRS ADL questionnaire was self-completed by study participants seated in a waiting room, and each item was reviewed by the senior author (YK) at the beginning of each participant's examination. The UPDRS Motor subscale includes five domains: *tremor* (UPDRS Tremor: resting tremor and action or postural tremor); *rigidity* (UPDRS Rigidity); *bradykinesia* (UPDRS Bradykinesia: finger-tapping, hand movement, rapid alternating movement, leg agility, ability to rise from a chair, gait, and body bradykinesia); *postural instability* (UPDRS Posture: posture and postural instability); and "*other signs*" (speech and facial expression). Each test item of the UPDRS Motor subscale is scored in the range 0–4, where a higher score indicates a more severe problem. The UPDRS Motor test was administered by an occupational physician (YK) who has specialized in the assessment of Mn-exposed workers for over 15 years.

2.4. Postural sway

Postural sway was measured using the CATSYS 2000 (Coordination Ability Test System, Danish Product Development), according to standard procedures (Després et al., 2000). The postural sway analysis system consists of a platform containing three orthogonal strain-gauge devices. Postural sway was tested under four experimental conditions, in the following sequence: standing on the platform without foam underneath the feet [eyes open (EO) and eyes closed (EC)], and with foam underneath the feet [eyes open (FO) and eyes closed (FC)]. For each subject, postural sway was measured over 66 s. Several postural stability parameters were calculated, including mean sway, transversal sway, sagittal sway, sway area, sway intensity, and sway velocity. Mean sway is the simple mean of the distances from the mean force center position to all force center positions recorded during the test. Transversal sway and sagittal sway are the simple means of recorded x- and y-values of the force center in a coordinate system, respectively. Sway area is the area of the smallest polygon that includes the total trajectory of the force center in the horizontal plate plane of force. Sway velocity is defined as the average travel speed of the force center in the horizontal force plate plane divided by the total length of the force center trajectory (in millimeters) within the recording period. Sway intensity is defined as the root mean square value of acceleration, recorded in the 0.1–10.1 Hz band during the test period.

2.5. Questionnaire

Participants were asked to submit a list of current medications and to fill out a health questionnaire assessing symptoms, illnesses, work and residential history, and daily living habits. Medications and illnesses were categorized into ICD9 categories.

All participants were administered a test of effort and if results were questionable, the participant was administered a more lengthy test of effort and symptom validity. All of the participants passed these sensitive tests of effort and malingering (Bowler et al., in this issue).

2.6. Blood biomarkers

Certified phlebotomists drew a blood sample from each participant. Serum was analyzed for ferritin level [as a biomarker of iron (Fe) status] and the activities of two hepatic enzymes [serum alanine aminotransferase (ALT) and serum gamma-glutamyltransferase (GGT)]. Abnormal values of such biomarkers may indicate compromised Mn homeostasis. The levels of the neurotoxic metals Mn, mercury (Hg), lead (Pb), and cadmium (Cd) were assayed in whole blood. Serum samples were frozen during storage and shipment, and were analyzed at the Analytical Chemistry Core of the US-EPA (Research Triangle Park, NC). Whole blood samples were cooled during storage and shipment, and were analyzed at the National Center for Environmental Health Laboratory of the CDC (Atlanta, GA). The accuracy of the biomarkers is assured by the stringent quality assurance/control policies in place at the Analytical Chemistry Core of the USEPA (Research Triangle Park, NC) and the National Center for Environmental Health Laboratory of the CDC (Atlanta, GA).

2.7. Statistical analysis

Univariate distributions of continuous variables were examined to evaluate normality using the Kolmogorov–Smirnov test. To better attain normal distributions, some variables were log-transformed. In most instances, arithmetic mean (AM) and standard deviation (SD) are shown. The mean values of several continuous variables were compared using Student's t-test. Differences in the proportions of smokers, the proportions of those in individual income groups, and the percentages of those who were unemployed, uninsured or white, were evaluated using the Chi-square test. Because of markedly skewed distributions, the Mann–Whitney U-test was employed to test differences in UPDRS scores between participants in the two towns. The UPDRS scores were dichotomized (thus, any score greater than zero was considered to be abnormal). Having multiple participants from the same households did not affect motor examination outcomes. The results of the main analyses were not different when multiple participants from the same households were removed. In addition, the effect size was computed. In the study design phase, power analysis indicated the sample size was sufficient to detect a 40% (or 0.4) effect size of between-group differences on test scores. The effect size was defined as the ratio of the difference of any two means to the pooled standard deviation. The latter figure was computed by obtaining the square root of the weighted mean of the two sample variances, with the weight being equal to the sample size minus 1. This is equivalent to the Cohen's d effect size definition. An effect size of 0.40 was considered to be medium by Cohen (1988). We calculated adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for abnormal UPDRS parameters (scores > 0) of the ADL, Motor, and Bradykinesia subscales using logistic regression (Mn-exposed vs. comparison town). In Model 1, adjustment was made for age, sex, ethnicity, smoking status, drinking status (alcohol), educational level, household income, and insurance status. In Model 2, adjustment for log values of serum ferritin, ALT, and GGT; body mass index (BMI); history of musculoskeletal, neurologic, and/or mental illness; and mental and/or neuroleptic medication histories were made in addition to the covariates of Model 1. To evaluate the additional effect of metals on the prevalence of abnormal UPDRS scores, we included the blood levels of three metals (Pb, Cd, and Hg) as covariates, in addition to the covariates of Model 2 (Model 3). We also assessed the effect of exposure status (Mn-exposed town vs. comparison town) by multiple regression analysis, employing postural sway parameters as dependent variables after controlling for various covariates. B-coefficient values and 95% CIs of log-transformed

postural sway variables with respect to study group (exposure vs. comparison) were presented. In Models 1–3, adjustment was made for various covariates in the same manner as in logistic regression. Missing data in any (co)variable included in the multivariate analyses were deleted listwise.

3. Results

Table 1 summarizes the demographic characteristics of the Mn-exposed and comparison groups. There was no between-group difference in age, sex, average years of residency or education, smoking or drinking status, BMI, household income (% of those in each income group), or proportion of those unemployed or uninsured. In addition, participants in both groups were predominantly white.

Table 1 also shows the exposure indices and clinical laboratory data (biomarkers) for both groups. The average concentration of Mn-B was similar in the participants of both towns (exposed: 9.65 μg/L, comparison: 9.48 μg/L), and these values were well within the normal range of 4–15 μg/L (ATSDR, 2008). Few Mn-B values were above the limit of the upper range (exposed: $n = 6$; comparison: $n = 7$). Very few participants had low serum ferritin levels (exposed: $n = 2$; comparison: $n = 2$). In general, hepatic enzyme activities in serum were normal. However, a few exceptions (with elevated levels) were noted; these subjects did not have an abnormal Mn-B concentration. ALT was elevated in one subject of each group; GGT levels were high in two subjects of the exposed and three of the comparison group. Our previous studies showed that mere changes in hepatic enzyme activities without portal systemic shunt as in liver cirrhosis did not influence the metabolism of Mn (Bang et al., 2007; Choi et al., 2005; Park et al., 2003). The values of the biomarkers of exposure to other neurotoxic metals did not differ between groups, and no overexposure to such metals was evident. The participants in Marietta resided, on average, 4.75 miles from the Mn point source. The modeled residential Mn-air estimates ranged from 0.04 to 0.96 μg/m^3, and averaged 0.18 μg/m^3.

Fig. 1 compares the distribution of UPDRS scores between the two groups. No difference in UPDRS ADL scores was evident. The overall means of the UPDRS Motor and Bradykinesia scores were significantly higher in the exposed group than in the comparison group. However, the effect sizes were small (Motor: 0.22; Bradykinesia: 0.20). No participant was diagnosed with clinical manganism on neurological examination. Correlation coefficients (Spearman's rho) of UPDRS Motor scores with UPDRS Bradykinesia and UPDRS ADL scores were 0.717 ($p < 0.01$), 0.342 ($p < 0.01$), respectively. Spearman's rho correlation coefficient of UPDRS Bradykinesia scores with UPDRS ADL scores was 0.413 ($p < 0.01$). However, UPDRS Motor or Bradykinesia scores did not correlate with exposure indices such as Mn-B, or modeled air-Mn (data not shown).

Table 1
Demographics, biomarkers, and air manganese exposure indices, by study group.

Characteristics	Marietta (exposed, $n = 100$)				Mount Vernon (comparison, $n = 90$)				p-Value
	n	Mean ± SD	Median	Range	n	Mean ± SD	Median	Range	
Demographics									
Age (years)	100	54.4 ± 9.9	55.5	30.0–74.0	90	55.5 ± 11.0	55.5	32.0–75.0	0.462
Years of education	100	14.6 ± 2.7	14.0	8.0–22.0	90	15.2 ± 3.0	14.0	12.0–22.0	0.130
Years of residence	100	36.1 ± 15.8	37.0	10.0–65.0	90	33.6 ± 17.2	31.0	10.0–74.0	0.291
Sex									0.939
Male	45				40				
Female	55				50				
Current smoker	20				18				1.000
Weekly alcohol consumption (g)	94	31.7 ± 63.9	0.0	0.0–392.4	85	29.2 ± 61.6	0.0	0.0–362.1	0.786
Annual household income									0.745
$0–29,999	26				14				
$30,000–59,999	28				32				
$60,000–89,999	19				19				
$90,000 or above	19				19				
Not recorded	8				6				
Work history									0.078
Employed	63				61				
Unemployed or retired	31				28				
Disabled	6				0				
Not recorded	0				1				
Uninsured	12				17				0.228
White	94				87				0.503
BMI (kg/m^2)	92	29.4 ± 7.0	28.2	15.6–54.0	90	29.1 ± 7.0	30.0	16.5–51.4	0.825
Biomarkers									
Blood Mn (μg/L)	100	9.65 ± 3.21	9.15	4.91–24.60	90	9.48 ± 3.16	8.79	3.75– 18.90	0.702
Males	45	8.80 ± 1.90	8.60	5.10–12.50	40	9.20 ± 3.20	8.50	5.21–18.72	0.524
Females	55	10.32 ± 3.93	9.49	4.94–24.58	50	9.71 ± 3.09	9.26	3.77–18.92	0.361
Blood cadmium (μg/L)	100	0.53 ± 0.53	0.31	0.14–2.87	90	0.47 ± 0.54	0.30	0.00–4.06	0.455
Blood mercury (μg/L)	100	1.38 ± 1.89	0.77	0.23–14.60	90	0.96 ± 1.26	0.66	0.23–9.75	0.078
Blood lead (μg/L)	100	15.6 ± 9.5	13.0	3.2–53.9	90	14.1 ± 9.5	11.4	3.1–59.6	0.277
Serum ferritin (μg/L)	100	132.2 ± 153.3	76.3	12.2–858	90	130.6 ± 111.2	89.9	7.7–554	0.941
Males	45	189.6 ± 180. 3	129.0	14.3–858	40	179.4 ± 131.2	141.5	7.7–554	0.770
Females	55	85.2 ± 107.5	62.5	12.2–639	50	91.7 ± 72.7	64.5	95.0–329	0.722
Serum ALT (IU)	100	14.9 ± 6.7	15.0	5.3–55.5	89	15.0 ± 6.3	15.1	0.0–37.9	0.938
Serum GGT (IU)	100	18.6 ± 9.1	20.0	8.0–73.9	89	18.3 ± 7.8	20.0	8.2–72.5	0.796
Exposure indices									
Distance from point source (miles)	100	4.75 ± 1.64	4.50	0.99–11.00					
Modeled Mn-air (μg/m^3)	100	0.18 ± 0.13	0.16	0.04–0.96					

ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; Mn, manganese.

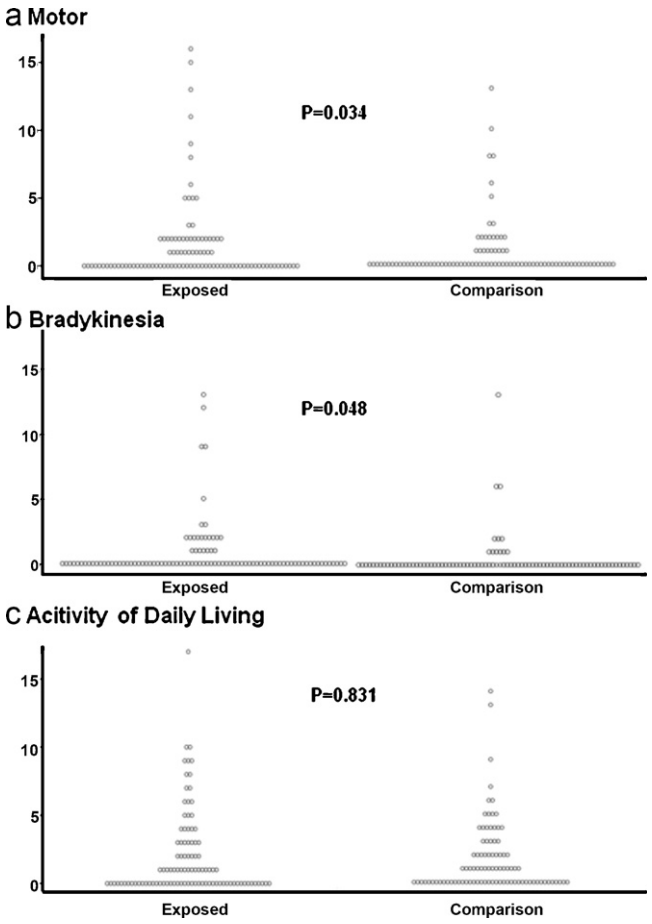

Fig. 1. Distribution of UPDRS data of the exposed ($n = 99$) and comparison town participants ($n = 90$). *Y*-axis is the scale of UPDRS scores. *p*-Value by Mann–Whitney *U* test; UPDRS Motor and Bradykinesia scales assessed by physical examination: Activity of Daily Living scales by interview.

Table 2 shows the adjusted ORs and 95% CIs for abnormal UPDRS ADL, Motor, and Bradykinesia parameters (scores > 0) obtained by logistic regression (Mn-exposed vs. comparison town). In Model 1, after adjusting for the covariates age, sex, ethnicity, smoking status, drinking status (alcohol), educational level, household income, and insurance status, the risks of abnormal UPDRS Motor and Bradykinesia scores were in the exposed group respectively 2.43- and 2.90-fold higher than in the comparison group. Including of other covariates (Models 2 and 3) did not change the ORs for abnormal UPDRS Motor scores. However, the risk of abnormal UPDRS Bradykinesia scores increased by 52% and 79% after further adjustment using the additional covariates of Models 2 and 3, respectively. The risk of abnormal UPDRS ADL in the exposed group was not elevated in any of the models.

Table 2
Odds ratios (ORs) and 95% confidence intervals (CIs) for the presence of abnormal UPDRS findings (scores > 0) with respect to study group (exposed vs. comparison town), after adjustment for covariates ($n = 166$).

Outcome variable		OR (95% CI)	*p*-Value
UPDRS ADL > 0	Model 1	0.99 (0.526–1.872)	0.981
	Model 2	0.79 (0.383–1.615)	0.513
	Model 3	0.74 (0.347–1.558)	0.422
UPDRS Motor > 0	Model 1	2.43 (1.176–5.021)	0.016
	Model 2	2.52 (1.111–5.729)	0.027
	Model 3	2.42 (1.038–5.648)	0.041
UPDRS Bradykinesia > 0	Model 1	2.90 (1.181–7.096)	0.020
	Model 2	4.41 (1.383–14.047)	0.012
	Model 3	5.18 (1.520–17.635)	0.009

Model 1: adjustment for age, sex, ethnicity, smoking status, drinking status (alcohol), educational level, household income, and insurance. Model 2: log serum ferritin, ALT, and GGT; any history of musculoskeletal, mental and/or neurologic illness; BMI; and mental and/or neuroleptic medication history were included as covariates to those of Model 1. Model 3: log blood lead, cadmium, and mercury were additionally included to the covariates of Model 2. Missing data in any (co)variable included in the analyses were deleted listwise.

Table 3 shows differences in postural sway parameters between the two groups. Among EO postural sway parameters, mean and sagittal sway, and sway intensity were significantly higher in the exposed than in the comparison group, while among FO postural sway parameters, mean and sagittal sway were significantly higher in the exposed compared to comparison group. The effect sizes were small to medium (0.23–0.42). Under the EC or FC condition, no difference in any sway parameter was evident between the two groups (data not shown). There was no significant correlation between Mn-B or modeled air-Mn levels and any postural sway parameter (data not shown).

Table 4 shows the *B*-coefficients obtained by multiple regression analysis modeling postural sway after adjustment for covariates. In Model 1, after adjustment for age, sex, ethnicity, smoking status, drinking status (alcohol), educational level, household income, and insurance status, mean sway (EO), sagittal sway (EO), sway area (EO), sway intensity (EO), mean sway (FO), sagittal sway (FO), sway area (FO), and sway velocity (FO) were significantly higher in the exposed group than in the comparison group. Abnormal postural sway parameters remained almost unchanged after further adjustment for covariates [Model 2: effect modifying biomarkers (serum ferritin and hepatic enzymes) and

Table 3
Postural sway of the study participants in the Mn-exposed and comparison town.

		Marietta (Mn-exposed, $n = 99$)			Mount Vernon (comparison, $n = 90$)			*p*-Value*	Effect size
		Mean ± SD	Median	Range	Mean ± SD	Median	Range		
EO	Mean sway (mm)	4.69 ± 1.51	4.5	2.5–14.7	4.34 ± 1.56	4.0	2.0–12.5	0.039	0.228
	Transversal sway (mm)	2.59 ± 1.14	2.5	1.4–11.9	2.53 ± 1.11	2.3	1.0–9.8	0.483	0.053
	Sagittal sway (mm)	3.33 ± 1.03	3.3	1.4–6.2	2.96 ± 1.08	2.8	1.4–7.5	0.006	0.350
	Sway area (mm^2)	233.43 ± 191.14	203.0	79.0–1707	222.6 ± 212.3	176.5	44.0–740	0.210	0.053
	Sway intensity	4.00 ± 1.07	3.85	2.39–8.63	3.72 ± 1.26	3.5	1.58–7.04	0.027	0.239
	Sway velocity (m/s)	9.35 ± 2.96	8.8	5.2–21.1	9.33 ± 4.02	8.2	4.5–24.3	0.537	0.006
FO	Mean sway (mm)	6.03 ± 1.41	5.8	3.5–10.1	5.63 ± 1.25	5.5	3.2–9.2	0.042	0.301
	Transversal sway (mm)	3.23 ± 0.82	3.2	1.5–5.8	3.17 ± 0.80	3.2	1.8–5.3	0.667	0.074
	Sagittal sway (mm)	4.39 ± 1.15	4.2	2.3–7.9	3.94 ± 0.99	3.9	1.9–6.4	0.005	0.421
	Sway area (mm^2)	391.78 ± 193.41	347.5	146.0–1080	361.5 ± 207.5	315	122.0–1120	0.127	0.151
	Sway intensity	5.41 ± 1.55	5.1	2.70–13.25	5.26 ± 1.69	4.96	2.91–10.39	0.322	0.092
	Sway velocity (m/s)	12.92 ± 4.25	12.3	5.9–27.6	12.20 ± 6.09	10.8	5.8–51.6	0.068	0.136

EO: eyes open, without foam; FO: eyes open, with foam.
* *p*-Values were calculated after logarithmic transformation.

Table 4
B-coefficient values and 95% confidence intervals (CIs) of log-transformed postural sway variables with respect to study group (Mn-exposed vs. comparison) in multiple linear regression analysis models after adjustment for covariates[a] ($n = 157$).

Dependent variable	Study group (Mn-exposed vs. comparison town)		
	Model 1	Model 2	Model 3
Log mean sway (EO)	0.133 (0.044–0.221)*	0.125 (0.030–0.220)*	0.116 (0.017–0.216)*
Log transversal sway (EO)	0.075 (−0.022 to 0.173)	0.082 (−0.022 to 0.186)	0.085 (−0.024 to 0.195)
Log sagittal sway (EO)	0.173 (0.074–0.271)*	0.150 (0.044–0.257)*	0.137 (0.026–0.248)*
Log sway area (EO)	0.198 (0.024–0.372)*	0.206 (0.024–0.388)*	0.187 (−0.002 to 0.377)
Log sway intensity (EO)	0.131 (0.046–0.216)*	0.155 (0.066–0.244)*	0.142 (0.050–0.234)*
Log sway velocity (EO)	0.083 (−0.008 to 0.175)	0.096 (0.007–0.186)*	0.096 (0.003–0.190)*
Log mean sway (FO)	0.096 (0.028–0.163)*	0.087 (0.017–0.157)*	0.078 (0.006–0.151)*
Log transversal sway (FO)	0.044 (−0.032 to 0.119)	0.036 (−0.045 to 0.118)	0.039 (−0.047 to 0.124)
Log sagittal sway (FO)	0.132 (0.053–0.211)*	0.120 (0.038–0.203)*	0.109 (0.024–0.194)*
Log sway area (FO)	0.171(0.031–0.311)*	0.157 (0.011–0.303)*	0.164(0.010–0.318)*
Log sway intensity (FO)	0.068 (−0.019 to 0.155)	0.075 (−0.018 to 0.167)	0.085 (−0.012 to 0.182)
Log sway velocity (FO)	0.132 (0.037–0.226)*	0.134 (0.044–0.224)*	0.141 (0.045–0.236)*

Missing data in any (co)variable included in the analyses were deleted listwise statistically.
* $p < 0.05$ in terms of both *B*-coefficients and model fit.
[a] Model 1:adjustment for age, sex, ethnicity, smoking status, drinking status (alcohol), educational level, household income, and insurance status. Model 2: log serum ferritin, ALT, and GGT; any history of musculoskeletal, mental and/or neurologic illness; BMI; and mental and/or neuroleptic medication history were included as covariates to those of Model 1. In Model 3: log blood lead, cadmium, and mercury were additionally included to the covariates of Model 2.

factors potentially influencing motor performance (BMI; history of musculoskeletal, neurologic, and/or mental illness; and mental and/or neuroleptic medication history)] or Model 3 (blood levels of Pb, Cd, and Hg). Most of these sway parameters correlated with age after adjusting for other covariates (data not shown).

In terms of particular illnesses, the only significant between-group difference was that more subjects in the comparison town had been diagnosed with pneumonia (27.8% vs. 14.0%). Illnesses in other ICD9 categories did not significantly differ in frequency between groups (data not shown).

4. Discussion

The present study examined the motor function and postural stability of residents of an Ohio community exposed to long-term, low-level environmental Mn in the air, and compared the findings with data from residents of a community not subject to Mn exposure. No between-group difference in demographics, blood/serum biomarkers, or Mn-B level was evident. Modeled Mn-air level (respirable) in the Mn-exposed town ranged 0.04–0.96 $\mu g/m^3$ and amounted on average to 0.18 $\mu g/m^3$ which is 3.6 times more than the current US-EPA RfC of 0.05 $\mu g/m^3$. The WHO stated in 1981 that the annual average Mn levels in urban non-polluted areas ranged from 0.01 to 0.03 $\mu g/m^3$, whereas, in industrial urban areas, the levels were elevated to 0.01–0.07 $\mu g/m^3$. In the vicinity of foundries, the levels were 0.2–0.3 $\mu g/m^3$, and towns with ferroalloy industries registered over 0.5 $\mu g/m^3$ (WHO, 1981). Average Mn concentrations in $PM_{2.5}$ air samples taken outside a ferroalloy plant in Italy were as high as 0.7 $\mu g/m^3$ and averaged 0.08 $\mu g/m^3$ at about 50 km downwind (Lucchini et al., 2007). The modeled Mn-air levels for the Marietta site in the present work are in line with the Mn-air levels recorded in these studies, but they are much higher than the ambient Mn-air levels reported for Southwest Quebec (range, 0.009–0.035 $\mu g/m^3$; mean, 0.022 $\mu g/m^3$) (Hudnell, 1999). However, compared to currently reported occupational Mn exposures, the Mn-air levels to which the Marietta participants were exposed during the last decade were at least two orders of magnitude lower. Note also that the Mn-B distribution in the Marietta participants did not differ from that in the participants of the comparison town Mount Vernon. Whole Mn-B is known to be unreliable as an individual biomarker of Mn exposure (Lucchini and Kim, 2009), but in the present study it does not seem to be a useful surrogate biomarker for long-term low-level Mn exposure even on a group basis. A better biomarker of chronic Mn exposure appears to be bone Mn measurement by X-ray fluorescence spectroscopy (Zheng et al., 2011), but unfortunately, aspects of study design and financing did not allow us to use this measure.

Mn is an essential element and its blood circulation, more specifically in the plasma compartment (the most biologically readily available Mn for accumulation in the brain), is actively controlled by the homeostatic mechanism regulating absorption, distribution, and excretion of the Mn^{2+} ion. A recent study in Mn-exposed welders showed that current exposure to Mn-containing welding fumes (Mn-air: GM, 27.7 $\mu g/m^3$; range, 1.3–729 $\mu g/m^3$) did not change the plasma-Mn concentration when Mn-air remained below 10 μg Mn/m^3 (Hoet et al., 2011). Recently developed pharmacokinetic models in non-human primates and humans indicate that inhalation exposure to respirable $MnSO_4$ particulate at levels below 10 μg Mn/m^3 is not expected to lead to Mn^{2+} accumulation in the globus pallidus (Andersen et al., 2010; Schroeter et al., 2011). Since increased concentrations of plasma-Mn are not expected for Mn-air exposure below 10 μg Mn/m^3, the likelihood of Mn accumulation in the brain and the biologically plausibility of subsequent neurological disruption does not seem very high. Associations between Mn-air and adverse CNS effects are thus unlikely to occur in Marietta participants, as there is no reason to believe that their chronic Mn exposure conditions would entail increased plasma Mn levels. Taken together, the long-term low-level environmental Mn-air exposure most likely represented for Marietta participants a much lower risk for clinical illness than for subjects occupationally inhaling Mn.

The UPDRS is widely used to measure the presence and severity of parkinsonian signs among individuals with PD (Jankovic et al., 1990; Parkinson Study Group, 1993), but it is also used to document parkinsonian features in subjects without PD (Bennett et al., 1996, 1997; Bowler et al., 2007b; Koller et al., 2004; Richards et al., 1993). In the present study no association was found between Mn-B values and UPDRS data or postural sway, although we found subclinical motor and sway deficits in Marietta residents compared to those in Mount Vernon. The risk of scoring abnormally (score > 0) on the UPDRS Motor and Bradykinesia subscales was significantly higher in the exposed group than in the comparison group, even after adjustment for potential covariables as used in the Models 1, 2, and 3 (Table 2). These results reveal that it were principally UPDRS Bradykinesia components which influenced the UPDRS scale values rather than the tremor or rigidity components of UPDRS Motor. No participant of Marietta was diagnosed with clinical manganism upon neurological examination. Taken together with the small effect

sizes of the UPDRS differences between the exposed and comparison participants, these findings may indicate early subtle subclinical motor function deficits in Marietta participants due to long-term low-level Mn exposure.

Postural balance is a complex task that is controlled by both the central and peripheral nervous systems. Maintaining upright posture requires integration of brain sensory inputs and motor outputs controlling the body musculature to achieve appropriate coordination. Under EO conditions, visual, proprioceptive, and vestibular pathways yield sensory information relevant to maintain the postural balance. Upon testing under EC conditions, the visual pathway is sidelined, leading to increased dependence on proprioceptive and vestibular inputs. Under FO conditions, a subject stands on foam to reduce proprioceptive input and to increase dependence on visual and vestibular inputs. The FC condition reduces both visual and proprioceptive inputs, focusing maximum reliance on vestibular function (Balasubramaniam and Wing, 2002). Postural instability has been associated with Mn neurotoxicity in occupational or environmental settings (Bowler et al., 2007a,b; Chia et al., 1993, 1995; Hudnell, 1999; Kaji et al., 1993; Kim et al., 2007; Myers et al., 2003; Young et al., 2005). Standridge et al. (2008) reported increased postural sway values in a small group of participants of the Marietta community ($n = 22$, not chosen at random and different from those investigated in the present study) in comparison to controls (also selected in a non-random manner). In the present work, we randomized subject selection, and found that subjects in the exposure group showed significant increases in many postural sway parameters compared with the comparison group, after potential confounders were adjusted for. Using the Danish Product Development CATSYS sway test, Myers et al. (2003) found significantly higher sway values in Mn-exposed smelter workers than in referents under test conditions of eyes open (EO and FO), but not under test conditions with eyes closed. Our finding of increased postural sway in the eyes open test condition is in line with these results. However, other studies on workers exposed to higher levels of Mn-air showed worse postural stability when eyes were closed (Bowler et al., 2007a,b; Chia et al., 1993). The reasons of the discrepancies for the eyes closed/open conditions are yet unknown to the authors, and need further study.

In the present study, older age was associated with an increase in postural sway which is compatible with findings of decreased postural control in the elderly as a result of reduced visual acuity (Lord and Menz, 2000) and poorer receipt of proprioceptive information (Goble et al., 2009). Changes in sagittal sway were more significant than were those in transversal sway, which is in agreement with data on manganism patients who exhibit a propensity to fall backwards (Calne et al., 1994; Feldman, 1999). Despite the presence of subclinical abnormalities detected for postural sway with the CATSYS, the clinical postural instabilities noted during the UPDRS tests did not differ significantly between the exposed and comparison groups. Our findings most likely reveal functional subclinical impairment, probably associated with vestibular, visual, or proprioceptive sensory afferents in the exposed group. One of the important functions of the basal ganglia is integration of sensory feedback from the visual, proprioceptive, and vestibular systems (Visser and Bloem, 2005). It is plausible that our subclinical findings of increased postural sway reflect early neurotoxic effects of Mn in these brain regions. Slowed movement (Bradykinesia), alteration in gait, and a propensity to fall backwards are cardinal signs of manganism (Calne et al., 1994; Feldman, 1999). Taken together, the results in the Mn-exposed group indicate that subclinical impairment of postural stability control and motor function, shown by abnormalities in UPDRS scores and CATSYS recordings of postural sway, may be attributable to early subtle effects of long-term low-level environmental Mn exposure.

The present epidemiological investigation had strengths and limitations. We randomly selected participants, using appropriate and strict inclusion/exclusion criteria, to enable generalization of the data to adult residents who had lived for more than 10 years in a Mn-exposed community. As in any community-based study, we could not control which subjects would return the response cards indicating willingness to participate. Subjects to whom invitations were sent, were randomly chosen, however, those who responded may not be a random sample of those who were mailed invitations to participate. We could not address this issue because we were unable to obtain data from nonparticipants. Although the two towns are demographically very similar and no difference in illness prevalence (except for more pneumonia in the comparison town) was evident, it remains to be confirmed in further studies whether subclinical motor dysfunction may be attributable either to Mn-related early neurotoxic effects or be the result of selection bias from the subjective concern of possibly being harmed by Mn exposure in the Marietta residents.

We compared two groups of participants (Marietta and Mount Vernon) and hypothesized that differences in UPDRS motor function between the groups are due to difference in Mn exposure status. We adjusted for possibly significant covariables when evaluating motor function as we controlled for (1) potential confounding by other neurotoxic metals (Cd, Hg, and Pb), (2) biomarkers of Mn effect modifiers, (3) factors that might affect motor performance, and (4) demographic confounders. However, we cannot completely rule out that these covariables might have contributed to the differences even if they were statistically adjusted for.

As no ambient Mn-air monitoring data were available for Mount Vernon, we could not corroborate the low background Mn-exposure status of the comparison town. Mount Vernon's appropriateness for comparison with Marietta was based on demographic similarities (U.S. Census Bureau, 2001a,b), as well as its low number of large industries (US-EPA, 2011a). Consequently, the Ohio EPA has no area air pollution control activities in Mount Vernon related to toxic metals and particulate emissions (Ohio EPA, 2010). For Mn emissions, Mount Vernon was shown to differ greatly from Marietta in the National Air Toxics Assessment, while Mn-air emissions for the Marietta study area were ranked among the highest in the U.S., with 99% attributed to point sources (US-EPA, 2010a). In the Mount Vernon area, Mn-air emissions were slightly above background models of long-range transport and from natural emission and other unknown sources (US-EPA, 2009a, 2011b). In Washington County, Mn-air emissions were ranked above the 95th U.S. percentile, while Knox County emissions were ranked below the 25th U.S. percentile (US-EPA, 2002, 2006). The lack of industrial airborne Mn emissions also precluded air dispersion modeling for Mount Vernon. The modalities of Mn exposure assessment for Marietta used in the present study have limitations as the modeled Mn-air may not reflect the actual Mn exposure level of each Marietta resident as would have been possible with personal air monitoring. It would have been optimal to have obtained Mn-air data for the many years of production by EMI to more accurately estimate a cumulative exposure index for Marietta residents. Further, daily migratory patterns of participants vary widely, potentially increasing or decreasing exposure frequency and duration. Since measured exposure data are superior to modeled data, the lack of correlation of the subtle motor function or postural sway deficits with Mn-air may be attributable to limitations of the model.

5. Conclusion

Because of too low Mn-air levels in Marietta, Mn-B concentrations did not differ between the participants living in Marietta and those living in the comparison town Mount Vernon. Nevertheless, after adjustment for covariates, UPDRS and postural sway scores

were worse in the Marietta participants compared with those of Mount Vernon. Subclinical effects on the UPDRS and postural sway scores in the Mn-exposed group may possibly reflect early subtle effects of chronic low-level Mn-air exposure. However, these early subtle effects observed in the present study might be due to chance, because the cross-sectional study design, the small to medium effect sizes, and the little biological plausibility are limiting the possibility of a causal relationship between the environmental Mn-air exposure and the early subclinical neurotoxic effects observed. Our findings are to some extent at variance with reports in the literature of adverse neurotoxic effects associated with low environmental Mn exposure (Hudnell, 1999; Lucchini et al., 2007; Mergler et al., 1999; Rodriguez-Agudelo et al., 2006). A prospective study with a larger sample size and if possible with higher environmental Mn exposure would be the appropriate study design to obtain conclusive results.

Conflict of interest

The authors declare that there are no conflicts of interest.

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DISCLAIMER STATEMENT

The views expressed in this manuscript are those of the authors and do not necessarily reflect the views or policies of the EPA or ATSDR.

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